High Production Volume (HPV) Challenge Program

201-16424A

Revised Test Plan

For

2,5-dihydrothiophene 1,1-dioxide (Sulfolene) CAS Number 77-79-2

Chevron Phillips Chemical Company LP
10001 Six Pines Drive
The Woodlands, Texas 77380

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ABBREVIATIONS

BCF = predicted bioconcentration factor
cm^3 = cubic centimeter
CPChem = Chevron Phillips Chemical Company LP
EC = Commission of the European Communities
HEW = (United States) Department of Health, Education, and Welfare
hPa = hectopascal
HPV = High Production Volume
ICCA = International Council of Chemical Associations
IUCLID = International Uniform Chemical Information Dataset
IUPAC = International Union of Pure & Applied Chemistry
Koc = organic carbon partition coefficients
LC_{50} = lethal concentration (to 50% of animals dosed)
LD_{50} = lethal dose (to 50% of animals dosed)
LOAELs = lowest observed adverse effect levels
mg/kg = milligrams per kilogram
mg/L= milligrams per liter
NOAELs = no observed adverse effect levels
OECD = Organisation for Economic Cooperation and Development
SIDS = Screening Information Data Set
Sulfolene = 2,5-dihydrothiophene 1,1-dioxide
USEPA = United States Environmental Protection Agency
µg = micrograms

I. EXECUTIVE SUMMARY

Chevron Phillips Chemical Company LP (CPChem) is committed to fulfilling the High Production Volume (HPV) Challenge Program commitments it made under the United States Environmental Protection Agency (USEPA) HPV Challenge Program on February 14, 2001. As part of this commitment, CPChem has volunteered to assess the health and environmental hazards, including selected physicochemical characteristics of 2,5-dihydrothiophene 1,1-dioxide (CASN 77-79-2), commonly known and referred to hereafter as Sulfolene. Sulfolene is a clear, solid, odorous organosulfur compound (C4H6O2S) used as a specialty solvent in petroleum refining and as a chemical intermediate in the production of tetrahydrothiophene 1,1-dioxide (Sulfolane).

CPChem has identified data from company proprietary files, peer-reviewed literature, and/or calculated endpoints using widely accepted computer modeling programs.

Physical/Chemical Properties
Physicochemical endpoints for Sulfolene are available for the purposes of the HPV Challenge Program by using existing measured data or data calculated by the EPIWIN© computer model. No additional testing is proposed.

Environmental Fate/Pathways
There are sufficient data to characterize the environmental fate of Sulfolene. An estimation from a Level III fugacity model predicts that this substance will likely partition to soil and water. Ready biodegradation testing shows that Sulfolene is not readily biodegradable and has very low predicted bioconcentration factors; organic carbon partition coefficients suggest similar fate profiles in the environment and no bioaccumulation hazard. Based on the chemical structure of Sulfolene, Sulfolene is not expected to undergo abiotic hydrolysis in the environment. No additional testing is proposed.

Ecotoxicity
The existing data on the acute toxicity of Sulfolene to fish, aquatic invertebrates, and aquatic plants are adequate to address the endpoints in the HPV Challenge Program. The data indicate that Sulfolene is relatively nontoxic to aquatic organisms. Fish appear to be the most sensitive species with a lethal concentration to 50% of dosed organisms (LC_{50}) of 940 milligrams per liter (mg/L). No additional testing is proposed.

Human Health Effects
The existing data on Sulfolene on the potential human health hazards are adequate to address the toxicity endpoints in the HPV Challenge Program for acute oral and inhalation toxicity, genotoxicity, repeated-dose toxicity, reproductive toxicity, and developmental toxicity. No additional testing is proposed.

Table 1 summarizes the test plan summary of sulfolene.

Table 1. Matrix of Adequate or Inadequate Data and/or Datagaps on Sulfolene

Test	Sulfolene Y/N (Klimisch Score)	Testing Planned? Y/N
Physical and Chemical Data		
Melting Point	Y (2)	N
Boiling Point	Y (2)	N
Vapor Pressure	Y (2)	N
Partition Coefficient	Y (1)	N
Water Solubility	Y (2)	N
Environmental Fate and Pathways		
Photodegradation	Y (2)	N
Stability in Water (Hydrolysis)	Y	N
Transport/Distribution	Y (2)	N
Biodegradation	Y (1)	N
Ecotoxicity		
Acute/Prolonged Toxicity to Fish	Y (1)	N
Acute Toxicity to Aquatic Invertebrates (*Daphnia*)	Y (1)	N
Acute Toxicity to Aquatic Plants (Algae)	Y (1)	N
Chronic Toxicity to Aquatic Invertebrates (*Daphnia*)	N	N
Toxicity		
Acute Toxicity (Oral)	Y (1)	N
Acute Toxicity (Inhalation)	Y (1)	N
Repeated Dose	Y (1)	N
GeneticToxicity *in vitro* – Gene Mutation	Y (1)	N
Genetic Toxicity *in vitro* – Chromosomal Aberration	Y (2)	N
Reproductive Toxicity	Y (1)	N
Developmental Toxicity	Y (1)	N

***NOTE*:**
The data used to characterize the Organisation for Economic Cooperation and Development (OECD) SIDS endpoints for substances in this test plan were identified either in company proprietary files, the peer-reviewed literature, and/or calculated using widely accepted computer modeling programs. All data were evaluated for study reliability in accordance with criteria outlined by the USEPA (1999). Only studies that met the reliability criteria of "1" (reliable without restrictions) or "2" (reliable with restrictions) were used to fulfill OECD SIDS endpoints. Additional data for Sulfolene is also included in the IUCLID (International Uniform Chemical Information Dataset), attached as Appendix I. A more detailed discussion of the data quality and reliability assessment process used in developing this test plan is provided in Appendix II.

II. GENERAL SUBSTANCE INFORMATION

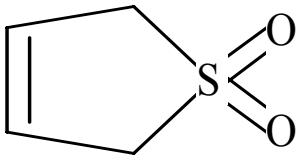
Sulfolene (CAS Number 77-79-2) is a commercially important product, with unique physical and chemical properties, that is used as an industrial solvent and isolated intermediate for the production of Sulfolane (CAS Number 126-33-0). Sulfolene is also used as a chemical intermediate in the production of transmission fluids.

Sulfolene is produced by the reaction of sulfur dioxide and 1,3-butadiene, and has a total production volume in the US of approximately 1.5 million pounds per year. Sulfolene is used commercially to remove benzene, toluene, and xylene from oil refinery streams and petroleum fuels, as well as to remove carbon dioxide from closed environments or scrubbing acids from various gas streams. A majority of Sulfolene is also subsequently hydrogenated to Sulfolane, another important solvent.

The structure of sulfolene is shown in figure 1.

Figure 1. Structure of Sulfolene

Sulfolene



International Union of Pure & Applied Chemistry (IUPAC) Chemical Name: 2,5-dihydrothiophene 1,1-dioxide

CAS Number = 77-79-2
Molecular Weight = 118.15
SMILES: O=S(=O)(CC=C1),C1

III. PHYSICOCHEMICAL PROPERTIES

The physical chemical data for Sulfolene provided in Table 2 were primarily obtained from well-established and scientifically accepted reference handbooks such as the Merck Index (O'Neil, 2001) the Industrial Solvents Handbook (Flick, 1985), and Hawley's Condensed Chemical Dictionary (Lewis, 2001), as well as EPIWIN-calculated values (USEPA and Syracuse Research Corporation, 2000).

Table 2. Measured (M) and Calculated (C) Physicochemical Properties

Test	M/C	Sulfolene
Melting Point	M[5,7]	63 - 65.5 ºC
	M[1]	64.5 ºC
	C[2]	17.43 ºC
Boiling Point	M[6]	Decomposes
	C[2]	201.11ºC
Vapor Pressure	M[9]	1.3 Pa at 25º C
	C[2]	VP: 0.132 mmHg (0.176 hPa)
Kow Partition Coefficient	M[8]	HPLC method < 1.0; Fragment addition Method = -0.8
	C[3]	-0.45
Water Solubility	M[5]	5.90 wt% at 25 ºC
	C[4]	2.879 x 10^5 mg/L

[1]EPIWIN v3.10; measured values from the EPIWIN experimental database.
[2]EPIWIN v3.10; calculated using MPBPWIN v1.40 (determined at 760 millimeter mercury [mmHg]).
[3]EPIWIN v3.10; calculated using KOWWIN v1.66.
[4]EPIWIN v3.10; calculated using WSKOW v1.40.
[5]Flick, 1985.
[6]Lewis, 2001 and Chevron Phillips, 2003.
[7]O'Neil, 2001.
[8]USEPA, 1991b.
[9] SafePharm, 2006

Summary: These data are considered adequate to meet the HPV Chemical Challenge requirements.

IV. EVALUATION OF ENVIRONMENTAL FATE DATA

Environmental fate data for Sulfolene were either experimentally measured or estimated using EPIWIN, and are provided in Tables 3 and 3a. Overall, Sulfolene is expected to be mobile if released to the environment, but will disappear based upon both biotic and abiotic degradation mechanisms and does not pose any bioaccumulation

hazard (as described below). In addition, Sulfolene is not expected to undergo abiotic hydrolysis in the environment based on its chemical structure.

Table 3. Measured (M) and Calculated (C) Results for Environmental Fate and Pathways

Test	M/C	Sulfolene
Photodegradation & Atmospheric Oxidation: • Ozone Rate Constant • Ozone Half Life • OH Rate Constant • OH Half Life	 C[1] C[1] C[1] C[1]	 20 x 10^{-17} cm^3/molecule-sec 1.375 Hrs. (at 7x 10^{11} mol/cm^3) 65.73 x 10^{-12} cm^3/molecule-sec 1.953 Hrs
Stability in Water (Hydrolysis)		No data. However, Sulfolene is not expected to undergo abiotic hydrolysis in the environment based on its chemical structure.
Transport/ Distribution Fugacity Estimated Koc: Estimated BCF:	 C[2] C[3]	 See model results below (Table 3a) 21.59 3.162
Biodegradation	M[4]	2% after 28 days 0% after 28 days

[1]EPIWIN v3.10; calculated using AOP Program v1.40.
[2]EPIWIN v3.10; calculated using PCKOC Program v1.66.
[3]EPIWIN v3.10; calculated using BCF Program v2.14.
[4]USEPA, 1991c.

Summary: These data are considered adequate to meet the HPV Chemical Challenge requirements. (See Table 3 and IUCLID documents).

A. Photodegradation-Atmospheric Oxidation

Values for Sulfolene photodegradation and atmospheric oxidation were calculated based upon chemical structures using EPIWIN and are shown in Table 3. A calculated half-life for Sulfolene of 1.375 hours and rate constant of 20 x 10^{-17} cubic centimeter ($cm^{3)}$/molecule-sec has been estimated for reaction with ozone. Also for reaction with hydroxyradicals, a calculated half-life for Sulfolene of 1.953 hours and a rate constant of 65 x 10^{-12} cm^3/molecule-sec has been estimated using EPIWIN.

Summary: These data are considered adequate to meet the HPV Chemical Challenge requirements.

B. Hydrolysis

Sulfolene is highly water soluble and is stable in solution. EPIWIN was unable to estimate a hydrolysis rate for the functional groups in Sulfolene. However, Sulfolene is not expected to undergo abiotic hydrolysis in the environment based on its chemical structure.

Summary: Although no data exists on the hydrolysis of Sulfolene, the chemical structure does not indicate that Sulfolene will undergo abiotic hydrolysis in the environment. These data are considered adequate to meet the HPV Chemical Challenge requirements.

C. Chemical Transport and Distribution in the Environment (Fugacity Modeling)

Tables 3a summarizes the Level III Fugacity results for Sulfolene produced by EPIWIN.

Table 3a. EPIWIN Level III Fugacity Results for Sulfolene

Compartment	100% to air	100% to water	100% to soil	Equally to each compartment
Air	69.6%	0.006%	0.03%	0.2%
Water	16.7%	99.8%	21.7%	55.9%
Soil	13.7%	0.001%	78.2%	43.8%
Sediment	0.03%	0.167%	0.04%	0.1%

Summary: Results from the Level III fugacity modeling indicate that releases to water would remain in water while releases to air and soil would partition to water and soil. These data are considered adequate to meet the HPV Chemical Challenge requirements.

D. Biodegradation and Bioaccumulation

Sulfolene has been tested in two Commission of the European Communities (EC)/OECD Ready Biodegradation tests, the Closed Bottle Test, and the Modified Sturm Test. The results are reliable without restrictions and fulfill the HPV SIDS endpoint for Sulfolene. The results are also in agreement with EPIWIN calculated results. Sulfolene should be inherently biodegradable under real world aerobic and anaerobic conditions. However, under the conservative conditions of the standard OECD ready tests, Sulfolene was shown not to be readily biodegradable.

For additional perspective, the EPIWIN predicted bioconcentration factor (BCF) and organic carbon partition coefficients (Koc) are identical and very low for Sulfolene, suggesting similar fate profiles in the environment and no bioaccumulation hazard.

Summary: These data are considered adequate to meet the HPV Chemical Challenge requirements. (See Table 3 and IUCLID documents).

V. ECOTOXICITY DATA

Acute fish, daphnid, and algal endpoints for Sulfolene are fulfilled with valid study data. The studies were conducted that are consistent with relevant OECD and USEPA guidelines. As shown in Table 4, Sulfolene is relatively nontoxic to aquatic organisms.

Aquatic studies have been performed on fish, aquatic invertebrates, and algae; fish appear to be the most sensitive species (LC_{50} = 940 mg/L for Sulfolene).

Table 4. Results for Ecotoxicity Endpoints

Test	Sulfolene
Acute/Prolonged Toxicity to Fish	96 hr LC_{50} = 940 mg/L[1]
Acute Toxicity to Aquatic Invertebrates (*Daphnia*)	24 hr EC_{50} > 1000 mg/L 48 hr EC_{50} = 800 mg/L[1]
Acute Toxicity to Aquatic Plants (Algae)	EC_{50} (growth rate) > 1000 mg/L[1]
Chronic Toxicity to Aquatic Invertebrates (*Daphnia magna* reproduction test)	No Data Available

[1]USEPA, 1991b.

Summary: These data are considered adequate to meet the HPV Chemical Challenge requirements. (see Table 4 and IUCLID document).

VI. HUMAN HEALTH EFFECTS

Sulfolene has a low order of toxicity by the oral and inhalation routes of exposure. It is not genotoxic based on the results of *in vitro* studies. Studies on repeated dose toxicity are inadequate for meeting the HPV Challenge Program requirements, and no reproductive or developmental toxicity exist for sulfolene.

Table 5. Results for Mammalian Toxicity Endpoints

Test	Sulfolene
Acute Oral	3006.5 mg/kg (m)[1]; 2547.3 mg/kg (f) [1] 2876.1 mg/kg (combined) [1]
Acute Inhalation	LC_{50}: greater than the saturated concentration in air at 25°C. No deaths reported in dose group.[2]
Repeated Dose	6 Week Study: Lowest observed adverse effect levels (LOAELs) for weight decrease: •Rat: 562 mg/kg/day (m); 178 mg/kg/day (f)[3] •Mouse: >3160 mg/kg/day (m); 316 mg/kg/day (f) [3] LOAELs for mortality: •Rat: >562 mg/kg/day (m); 316 mg/kg/day (f) [3] •Mouse: 1000 mg/kg/day (m); 1000 mg/kg/day (f) [3] No observed adverse effect levels (NOAELs) for weight decrease: •Rat: 316 mg/kg/day (m); 100 mg/kg/day (f) [3] •Mouse: >3160 mg/kg/day (m); 178 mg/kg/day (f) [3] NOAELs for mortality: •Rat: >562 mg/kg/day (m); 178 mg/kg/day (f) [3] •Mouse: 562 mg/kg/day (m); 562 mg/kg/day (f) [3] 28 Day Study: No observed effect level (NOEL) for lower mean body weights, body weight gains, and food consumption: •Rat: 25 mg/kg/day (m)[7] (f)[7]
Genetic – Gene Mutation	**A** – negative both with and without metabolic activation[4]; **B** – exp. to five graded doses with and without metabolic activation did not increase the reversion to histidine protrophy of five strains of *Salmonella typhimurium*[5]
Genetic – Chromosomal Aberration	Negative with and without metabolic activity[6]
Reproduction/ Developmental	No observed adverse effect level (NOAEL) for Reproductive Effects: • Rat: 75 mg/kg/day (f)[7], 150 mg/kg/day (m)[7] No observed adverse effect level (NOAEL) for Developmental Effects: • Rat: 25 mg/kg/day based on lower mean male and female pup weights[7]

[1] Hazleton, 1982a.
[2]USEPA, 1991a.[3] US Department of Health, Education, and Welfare [HEW], 1978.[4] Hazleton, 1982c.
[5] Hazleton, 1982d.[6] Loveday et al., 1990, [7]Wil Research, 2006..

Summary: These data are considered adequate to meet the HPV Chemical Challenge requirements.

A. Acute Toxicity

Acute toxicity studies show that Sulfolene is of low acute toxicity by both the oral and inhalation routes (oral LD_{50} = 2,876.1 mg/kg [combined male and female]; LC_{50} greater than the saturated concentration in air at 25°C) (see Table 5 and IUCLID document).

Summary: These data are considered adequate to meet the HPV Chemical Challenge requirements.

B. Repeated Dose Toxicity

A study was conducted to investigate the potential toxic effects of 3-sulfolene when administered to rats for 28 days (with a 14-day recovery period). The test article, 3-sulfolene, in the vehicle, Mazola® corn oil, was administered orally by gavage once daily to 3 groups of male and female Crl:CD(SD) rats. The low- and mid-dose groups each consisted of 12 rats per sex, and the high-dosage group consisted of 18 rats per sex. Dosage levels were 25, 75 and 150 mg/kg/day for males and 10, 25 and 75 mg/kg/day for females. Based on the lower mean body weights, body weight gains and food consumption at 75 mg/kg/day (males and females) and 150 mg/kg/day (males), a dosage level of 25 mg/kg/day was considered to be the NOEL for systemic toxicity.

Sulfolene has been tested in rats and mice by NCI in a oral gavage carcinogenicity study (HEW, 1978). In the 6-week range-finding study, only mortality and body weight effects were measured. The NOAELs for mortality were: 562 mg/kg/day for male rats and 178 mg/kg/day for female rats; and 562 mg/kg/day for both male and female mice. The NOAELs for weight decrease were: 316 mg/kg/day for male rats and 178 mg/kg/day for female rats; and >3160 mg/kg/day for male mice and 178 mg/kg/day for female mice.

Summary: These data are considered adequate to meet the HPV Chemical Challenge requirements.

C. Genetic Toxicity/Mutagenicity

1. Gene Mutation

Gene mutation tests conducted on Sulfolene have consistently resulted in negative results using the Ames/*S. typhimurium* test (Hazleton 1982b; 1982c).

2. Chromosomal Aberrations

In vitro chromosomal aberration test results were identified for Sulfolene (Loveday et al, 1990) which showed Sulfolene to be negative for the following categories of chromosomal aberrations:

- "simple," defined as a chromatid gap, break, fragment, and deletion or chromosome gap, break, or double minuets;
- "complex," defined as interstitial deletions, triradials, quadriradials, rings, and dicentric chromosomes; and
- "other," defined as pulverized chromosomes or cells with greater than 10 aberrations.

Summary: These data are considered adequate to meet the HPV Chemical Challenge requirements. (see Table 5 and IUCLID document).

D. Reproductive/Developmental Toxicity

A study was conducted to investigate the potential toxic effects of 3-sulfolene when administered to rats for 28 days (with a 14-day recovery period) and to evaluate the potential of 3-sulfolene to affect male and female reproductive performance such as gonadal function, mating behavior, conception, parturition and early postnatal development. The test article, 3-sulfolene, in the vehicle, Mazola® corn oil, was administered orally by gavage once daily to 3 groups of male and female Crl:CD(SD) rats. The low- and mid-dose groups each consisted of 12 rats per sex, and the high-dosage group consisted of 18 rats per sex. Dosage levels were 25, 75 and 150 mg/kg/day for males and 10, 25 and 75 mg/kg/day for females. Based on the lack of test article-related reproductive effects at 25, 75 and 150 mg/kg/day for males and at 10, 25 and 75 mg/kg/day for females, 75 mg/kg/day was considered to be the no-observed-adverse-effect level (NOAEL) for reproductive toxicity of 3-sulfolene when administered orally by gavage to Crl:CD(SD) rats. Based on the lower mean body weights, body weight gains and food consumption at 75 mg/kg/day (males and females) and 150 mg/kg/day (males), a dosage level of 25 mg/kg/day was considered to be the NOAEL for systemic toxicity. The NOAEL for neonatal toxicity was 25 mg/kg/day based lower mean male and female pup weights on PND 1 and 4 in the 75 mg/kg/day group.

Summary: These data are considered adequate to meet the HPV Chemical Challenge requirements.

VII. "BEYOND SIDS" ENDPOINTS

Studies have been performed on Sulfolene to investigate skin and eye irritation, and skin sensitization potential. A carcinogenicity study was also performed that demonstrated no significant increases in tumors in either sex compared to control groups (see IUCLID Document).

VIII. CONCLUSIONS

CPChem concludes that there are sufficient, reliable data on all of the HPV Challenge Program endpoints for Sulfolene, following a thorough review of company proprietary files, peer-reviewed literature, and/or calculated using widely accepted computer modeling programs.

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Appendix II

DATA QUALITY ASSESSMENT

Available environmental, ecotoxicity, and mammalian toxicity studies were reviewed and assessed for reliability according to standards specified by Klimisch et al., (1997), as recommended by the USEPA (1999a) and the OECD (OECD, 2002). The following reliability classification (Klimisch rating) has been applied to each study assessed:

- *1 = Reliable without Restriction* – Includes studies that comply with USEPA- and/or OECD-accepted testing guidelines and were conducted using Good Laboratory Practices (GLPs) and for which test parameters are complete and well documented;

- *2 = Reliable with Restriction* – Includes studies that were conducted according to national/international testing guidance and are well documented. May include studies that were conducted prior to establishment of testing standards or GLPs but meet the test parameters and data documentation of subsequent guidance; also includes studies with test parameters that are well documented and scientifically valid but vary slightly from current testing guidance. Also included in this category were physical-chemical property data obtained from reference handbooks, as well as environmental endpoint values obtained from an accepted method of estimation (e.g., USEPA's EPIWIN estimation program);

- *3 = Not Reliable* – Includes studies in which there are interferences in either the study design or results that provide scientific uncertainty or in which documentation is insufficient; and,

- *4 = Not Assignable* – This designation is used in this dossier for studies that appear scientifically valid but for which insufficient information is available to adequately judge robustness.

Those studies receiving a Klimisch rating of 1 or 2 are considered adequate to support data assessment needs in this dossier. Those key studies selected for inclusion are considered typical of the endpoint responses observed in other studies of a similar nature and design that were identified during our search of the literature.